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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,641	08/30/2001	Philip A. Beachy	JHUC-P01-017	9388

28213 7590 12/15/2004

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,641	BEACHY ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *2,3,6,7 and 33-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 8-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-32 in the reply filed on 17 October 2002 is acknowledged. The traversal is on the ground(s) that Groups II, V and VI depend on claim 1 of Group I. Applicants argue that Group III is directed to a method of identifying modulators of a mutated receptor (from Group I), and claims of Group IV are directed to transgenic animals using the mutated receptor (from Group I). This is not found persuasive because an application may properly be required to be restricted to two or more claimed inventions if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (i) or distinct (MPEP § 806.05 – § 806.05 (i)). The Examiner has shown that the Groups I-VI are independent or distinct inventions for the reason in the previous office action (see Paper mailed on 10/17/02). Furthermore, MPEP § 803 provides that the separate classification (i.e., class and subclass) of distinct invention is sufficient to establish a prima facie case that the search and examination of the plural inventions would impose a serious burden upon the Examiner. For example, Group I is a method of identifying mutations in a receptor, class 435, subclass 6, and Group IV is drawn to nonhuman animal, which is class 800, subclass 13. Further, searching for creating a transgenic animal and searching for a method of identifying a mutation would impose serious search burden. Searches for creating a transgenic nonhuman animal and a method of making mutation are not coextensive.

Applicant argues that the subject of species election is encompassed by a Markush group (claim5). Claim 5 is directed to a group of 7 transmembrane (7TM) receptors. These receptors comprise a group of hundreds, if not thousands, of 7TMs. These receptors are involved in associated in many diseases such as skin pigmentation, hunger control, metabolic disorders, central nervous system disorders. These receptors function independent of each other. Searches for all 7TMs and their biological function would impose serious burden. Searches for hundreds of 7TM and their biological functions are not coextensive.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election with traverse of species " G-Protein coupled receptor (GPCR), in the reply filed on 25 February 2003 is acknowledged.

Claims 2,3,6,7,33-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim.

Claims 1,4,5,8-32 are examined on the merits to the extent that they read on the elected species G-Protein coupled receptor (GPCR).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the

list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

One of the references cited in the information disclosure statement " Somers et.al." appears to have a typographical error. The Examiner reads the reference as " Sommers et.al." as recited in the reference article.

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: The word "tern yeast" on page 22, line appears to be typographical error and has been read as "term yeast".

Appropriate correction is required.

Claims 2,3,6,7, and 33-52 are objected to as encompassing non-elected subject matter. Amendment of the claims to delete the nonelected subject matter is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is vague and indefinite for recitation " measured indirectly". The metes and bounds of the recitation cannot be determined from the claim or the instant specification.

Claims 11-18 are indefinite for being directly or indirectly dependent from indefinite claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,4,5, 8-25, 27, 29-32 rejected under 35 U.S.C. 102(a) as being anticipated by Sommers et.al. (IDS, Biochemistry 39:6898-6909, 2000).

The claimed invention is drawn to method of identifying constitutive mutations of a candidate receptor or ion channel comprising providing a library of coding sequences for potentially activating mutations of a G protein coupled receptor, expressing the library in a host cell, measuring the activity of the encoded receptor or ion channels either directly by measuring the level of second messengers generated in response to receptor or ion channel or indirectly by measuring an indicator gene (heterologous reporter gene), wherein the indicator gene is modified by manipulating or replacing the promoter sequence at the natural locus of the indicator gene and is regulated by the receptor or ion channel in the host cell, and identifying the coding sequence responsible for at least 2, 5 or 10 fold activation of the receptor or ion channel.

Sommers et.al. teach a method for identifying constitutively activating mutations by making a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene (page 6899, left column, 2nd paragraph) in yeast and then screening for these mutations for the receptor activation. Sommers et.al. teach using either a direct method of binding 3H-[Nle12]α-factor to STE2 or an indirect method of monitoring a heterologous reporter system by combining the E.coli β-galactosidase gene (lacZ) under the yeast FUS1 promoter activated via the pheromone response pathway. Sommers et al. teach deleting the endogenous STE2 gene and providing external STE genes encoding several mutants of α-factor receptor to study the effects of various antagonists and agonists and to find out the amino acids responsible for switching a receptor between active and inactive stages (page 6898, right column, 1st paragraph). Sommers et.al. teach that introduction of mutations in an α-factor receptor (a yeast G protein coupled receptor) constitutively activate the receptor 2, 5, 7 (page 6902, left column, 2nd paragraph and right column, middle of the first paragraph), or 20 fold (page 6903, right column, 2nd paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,4,5,8, 10, 19-24, 26, and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et.al. (J. Neurochem. 69: 1138-1144, 1997) in view of Dahiyat et.al. (Science 278: 82-87, 1997).

The claimed invention is drawn to method of identifying constitutive mutations of a candidate receptor or ion channel comprising providing a library of coding sequences for potentially activating mutations of a G protein coupled receptor, expressing the library in a host cell, measuring the activity of the encoded receptor or ion channels either directly by measuring the level of second messengers generated in response to the receptor or ion channel or indirectly by measuring an indicator gene (heterologous reporter gene), wherein the indicator gene is modified by manipulating or replacing the promoter sequence at the natural locus of the indicator gene and wherein the indicator gene is regulated by the receptor or ion channel in the host cell. The claimed invention is further drawn to identifying the coding sequence responsible for at least 2, 5 or 10 fold activation of the receptor or ion channel and to replacing these large side-chain

amino acids with small or medium side-chain amino acids are located in or proximate transmembrane segement(s) of the receptor or ion channel.

Herrick-Davis et.al. teach application of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. They teach that the third transmembrane loop of the serotonin receptor (a G protein coupled receptor) is important for the inactivation state of the receptor. Herrick-Davis et al. teach that the mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT_2c receptor activates the receptor. Herrick-Davis et al. teach that the 5-HT_2c receptor mutants are expressed in mammalian expression vector pcDNA3 expression by transfecting the plasmid DNA into E. coli (page 1139, left column, last paragraph). They further teach transient transfection of COS7 (monkey kidney cell) cells with a mammalian expression vector (pcNDA3) and measurement of the hydrolysis of phosphotidylinositol as a result of activation from the serotonin receptor via a second messenger pathway (page 1139, left column, second and third paragraph, right column, last paragraph). Herrick-Davis et al. teach a 3 fold (S312K mutation) and a 30 fold (S312F mutation) increase in the binding affinity of 5HT to the mutant receptor (page 1140, left column, 3rd paragraph). Herrick-Davis et.al. do not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene.

Dahiyat et.al. teach a method of designing a protein library for the substitution of residues in any part of a protein including the buried core, the solvent exposed surface, and the boundary between core and surface (page, 82, 2nd paragraph). They teach that a protein sequence can be designed through a fully automated sequence selection process to accomplish a library of a protein having various changes in the amino acids (hydrophobic) within the core structure, side chains or in the amino acids (hydrophilic) on the surface of a protein (page 82, middle column, 1st paragraph). Dahiyat et.al. teach modifying core position amino acids using A, V, L, I, F, Y or W, modifying the surface amino acids using A, S, T, H, D, N, E, Q, K, or R (page 83, left column, continuing paragraph from page 82), whereas, the boundary position of a protein using a combination the amino acids as described above. Dahiyat et al teach that the automated sequence selection is an unbiased way of selecting amino acids for protein structure and function and that it is not limited to a particular motif or folding sequences.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to construct a library of coding sequences for potentially activating mutations at the interfaces between transmembrane helices using conserved residues of a candidate receptor gene using the site directed mutagenesis as taught by Herrick-Davis in view of Dahiyat. One of ordinary skill in the art at the time of invention was made would have found it prima facie obvious to have expressed the library in a host cell and to have measured the activity of the mutant receptor using the direct methods taught by Herrick-Davis. The person of ordinary skill in the art would have been motivated do so to more efficiently study the effect of various mutations in

side chain amino acids, within the residues of helical domain or the interfaces between transmembrane helices as taught by Dahiyat et al., for activating the receptor in order to increase the probability of finding novel therapeutic agents for antagonist, inverse agonist as taught by Herick-Davis et al (page, 1139, left column 2nd paragraph).

Claims 9, 11-18, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al in view of Dahiyat et al. as applied to claims 1,4,5,8, 10, 19-24, 26, and 29-32 above and further in view of King et.al. (Science 250: 121-123, 1990).

Herrick-Davis in view of Dahiyat et al. teach a method of identifying constitutive mutations of a candidate receptor or ion channel as set forth supra. Neither Herrick-Davis nor Dahiyat et.al. do teach a method of using a heterologous system to measure the activation of G-protein coupled receptor or ion channel.

King et.al. teach that the reconstruction of a heterologous reporter system using the β-galactosidase gene (lacZ) in yeast would elucidate understanding of a ligand binding to the G protein coupled receptor and its activation (page 123, left column, last paragraph). King et.al. teach that the mammalian β-aderenergic receptor is a 7TM receptor. They teach that a high level expression of the receptor in yeast is obtained by modifying the front end of the receptor with the NH2-terminual coding sequence of yeast STE2 gene and placing the receptor under GAL1 promoter. King et al teach constructing a heterologous reporter system by combining the E.coli β-galactosidase gene (lacZ) under yeast pheromone responsive FUS1 promoter to study G protein coupled receptor activation. Herrick-Davis, Dahiyat and King do not teach expression of

a library of coding sequences in a pigment cell to measure the activation through pigment dispersion or aggregation.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to make a heterologous reporter system as taught by King et.al. The person of ordinary skill in the art would have been motivated do so to measure the activation of G-protein coupled receptor or ion channel by measuring the change in blue color due to the expression of β-galactosidase gene as taught by King et al.

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et.al. (J. Neurochem. 69: 1138-1144, 1997) in view of Dahiyat et.al. and King et.al., as applied to claims 1, 4, 5,8-27 and 29-32 above and further in view of Lerner et.al. (US Patent NO. 6,051386).

Claim 28 is drawn to a eukaryotic cell as a pigment cell capable of dispersing or aggregating its pigment in response to an activated receptor or ion channels.

Herrick-Davis in view of Dahiyat et.al and King et.al. teach designing and making mutations within the coding sequences of a candidate G protein coupled receptor for the potential activation of the receptor using a library of coding sequences, and expressing the library in a host cell to measure the increased receptor activity by measuring a change in stimulus through a second messenger pathway as set forth supra. Herrick-Davis, Dahiyat and King do not teach the use of pigment cells to measure the pigment aggregation or dispersion in a pigment cell.

Lerner et.al. teach a method of identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. Lerner et al teach that certain chemicals and hormones make changes in signal transduction pathways that involve G-protein coupled receptors. These signal transduction pathways are reflected through changes in the level of cAMP or other second messengers. They teach that measurement of cAMP (by a direct method) or other messenger (by an indirect method) would facilitate antagonist or agonist identification. They teach that certain chemicals and hormones such as melanocyte stimulating hormone (MSH) and norepinephrine cause pigment dispersion, whereas, melatonin cause an increase in the pigment aggregation in a frog melanophores (column 11, line 17-24).

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to express the library of coding sequences taught by Herrick-Davis in view of Dayiat and king in a pigment cell to facilitate measurement through pigment dispersion and aggregation in response to a change in G-protein activation as is taught by Lerner et.al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
8 December 2004

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